Pulmonary Advisory Committee Meeting of May 15, 2003
Draft Topics for Discussion

Note: These are areas for your consideration in preparing for the May 15 Advisory Committee Meeting. We will likely be asking for discussion relating to these areas at the meeting. Multiple discussion topics are listed. Depending upon the discussion and advice relating to the topics addressed early in the course of the meeting, some later topics may become less important. A decision to defer some topics may be made during the meeting to ensure that adequate discussion is obtained on the most important issues.

1)
Genentech proposes the use of omalizumab in the treatment of allergic asthma among adults and adolescents. Genentech has submitted 4 randomized, placebo-controlled, double-blind studies of subcutaneous omalizumab use in allergic asthma; studies 008, 009, 010, and 011. Additional studies in allergic asthma patients include a phase 2 study relying on IV administration, and two controlled but open label trials designed primarily for safety assessments.

We would like discussion of the study results with attention to whether these studies provide substantial evidence of meaningful efficacy of omalizumab in the treatment of allergic asthma.

2)
Substantial fractions of patients screened for these studies were ineligible for enrollment due the presence of a baseline IgE concentration that was outside the permitted limits (either too high or too low) or their IgE concentration was too great for their specific body weight to fall within the range of IgE-weight permitted in the dosing table.

A discussion of the effect of these exclusions upon clinical practice will be useful. For example, patients whose IgE concentration value from a first test did not fall within a permitted dosing range could conceivably be evaluated with repeated retesting until a serum IgE concentration was obtained that did permit dosing.

Discussion of the expected stability or variability of IgE levels in allergic asthma may be valuable, especially as it applies to selecting patients for omalizumab therapy. Please include in your thinking whether the clinical study findings can be generalized to patients whose initial serum IgE concentrations preclude use of omalizumab therapy but repetitive testing ultimately results in the detection of an acceptable serum concentration.

3)
The expected stability or instability of serum IgE concentrations enters into assessment of this treatment in a second manner, when considering efficacy over long periods of time. The dosing of this treatment is based upon weight and pre-treatment IgE concentration. IgE levels cannot be re-evaluated while receiving omalizumab, or for an extended period after dosing is discontinued because the apparent serum IgE concentration is substantially altered by omalizumab. Efficacy has been evaluated only through 1 year of dosing.

Discussion relating to the stability of IgE levels in allergic asthma over long periods of time (e.g., years, relevant for the potential duration of treatment with omalizumab) will be useful. Please consider if planning a one-time evaluation of IgE concentration, leading to prolonged dosing based upon this one measurement, can be relied upon to ensure long-term efficacy of the treatment

4)
Subjects receiving certain common asthma medications were excluded from the majority of the studies. For example, Studies 008 and 009 excluded patients receiving any agent from among the following: leukotriene modifying agents, long-acting beta agonists, cromolyns, anticholinergics, oral steroids and xanthines. Study 011 allowed long-acting beta agonists and oral steroids, but excluded the other agents.

The findings of these studies may describe efficacy within a relatively narrow range of allergic asthma patients. Study 011 suggested little or no efficacy in patients receiving oral steroids.

Please consider and prepare for discussions to identify patient populations for which generalizations of efficacy may be reasonable. Populations to consider include (but need not be limited to):

- Subjects receiving only inhaled steroids
- Subjects receiving inhaled steroids irrespective of any other concomitant asthma controller medications
- Subjects receiving maintenance therapy with oral steroids

5)
If marketed, omalizumab would be the first passive immunotherapy for allergic asthma. Documentation of atopy (e.g., skin reactivity) is frequently required prior to active immunotherapy. The role of documenting aeroallergen reactivity prior to omalizumab therapy warrants discussion. Please recall that subjects enrolled in the major omalizumab safety and efficacy studies were required to have demonstrable skin reactivity to certain aeroallergens as a defining criterion of allergic asthma.

a) Please consider whether classifying a patient as having "allergic asthma" commonly requires a demonstration of skin reactivity at the present time within the general practice of pulmonary/allergy medicine. Specifically, please consider whether the type of therapy being considered (among those presently available) enters into the classification process.

b) Please consider whether the population of patients to whom the safety and efficacy of omalizumab can be generalized can be adequately described without an explicit reference to skin reactivity.

6)
Malignancies were an uncommon occurrence during clinical trials. However, the incidence of all malignancies was unequal between the treatment groups, with 20 events in approximately

3000 patient-years with omalizumab, and 5 events in approximately 1500 patient-years in control groups (rates of 6.3/1000 patient-years compared to 3.3/1000 patient-years). The rate increase of approximately 3 cancers per 1000 patient-years remained when examining cancers excluding non-melanoma skin cancer. Please give consideration to the strength of the evidence in establishing that there is or is not a risk of malignancy associated with this product. Please also consider the degree of emphasis that may be warranted in an advisement to the medical community regarding this issue.

7)
Anaphylaxis and/or important allergic reactions have been observed with this product. Please prepare for discussion regarding these observations and their importance in the setting of this disorder.

8)
A few published reports suggest IgE may have a role in mucosal immune function, and altered mucosal immunity may lead to adverse events. No excess in respiratory system adverse events was observed. However, an overall increase in digestive system adverse events largely without specific highlighted adverse event terms was observed. This increase did include an imbalance in the rate of appendicitis. Also observed was a small increase in the rate of female genitourinary adverse events, again largely without an ability to attribute this to specific adverse event types. Please discuss the importance of these events within the overall safety profile of this product.

9)
In addition to the above adverse events, rash was also observed with a small percentage increase in the omalizumab treated patients. Please prepare to discuss the significance of this finding.

10)
Certain aspects of the submitted safety database may place limitations on the interpretation of the results. For example, comprehensive data is limited to one year of omalizumab exposure. Additionally, the database contains only approximately 150 geriatric subjects treated with omalizumab. Please discuss the importance of these limitations, if any. Please discuss if these or other limitations or findings may necessitate the submission of additional data from the applicant prior to being able to form a risk-benefit assessment.

11)
Please give consideration to the overall risk-benefit comparison for the product and for which populations, if any, the comparison may be favorable.